THE ROCKEFELLER FOUNDATION

Meeting on Public-Private Partnerships in Biotech/Pharma
January 28-29, 1999, New York, NY

Agenda

The dinner on January 28th and meeting on January 29th will be held at:
The Rockefeller Foundation
420 Fifth Avenue, 22nd Floor, New York, NY 10018

Thursday, January 28

6:00 PM:	Cocktails
7:00PM:	Dinner: "The Rockefeller Foundation's experience in health products development." **Chair: Lincoln Chen**

Friday, January 29

8:00AM:	Continental Breakfast
8:15 AM:	**Chair: Tim Evans** Introductory remarks (**Gordon Conway**)
8:30 – 9:15AM:	Overview: • Discovery, development & distribution framework **(5 mins: Tim Evans)** • Current state of pharmaceutical and biotechnology industries: Where are market failures and gaps vis-à-vis infectious diseases? **(12 mins: Viren Mehta)** • Discussion **(25 mins: Chair: Tim Evans)**
9:15 – 10:30AM:	The discovery phase • Brief presentation **(12 mins: Graham Fagg, Wellcome Trust)** • Questions **(10 mins.)** • Discussion: ideas for partnerships in the discovery phase**(50 mins: Two breakout groups. Chairs: Steve Sinding and Gary Toeniessen)**
10:30 – 10:45AM:	Break
10:45– 12:00PM:	The development phase • Brief presentation **(12 mins: Charlie Arntzen, Boyce Thompson Institute)** • Questions **(10 mins)** • Discussion: ideas for public-private partnerships in the development phase **(50 mins: Two breakout groups. Chairs: Steve Sinding and Gary Toeniessen)**
12:00-12:30PM:	Lunch break
12:30 – 1:45PM:	Manufacturing & distribution • Brief presentation **(12 mins: Joe Cook, Edna McConnell Clark Fdn)** • Questions **(10 mins)** • Discussion: ideas for partnerships in manufacturing & distribution **(50 mins: Two breakout groups. Chairs: Steve Sinding and Gary Toeniessen)**

1:45 – 4:00PM: Final discussion **(Chair: Lincoln Chen)**:

- Reports from break-out groups (**5 min each**)
- Where are the barriers and opportunities for accelerating new product creation and introduction in infectious diseases?
- Potential public-private partnerships for philanthropy with industry.

4:00-4:20PM: Concluding remarks

- **Harold Varmus (5 mins)**
- **Ronald Saldarini (5 mins)**
- **Jurgen Drews (5 mins)**
- Wrap Up **(5 mins: Bill Foege)**

THE ROCKEFELLER FOUNDATION
Public-Private Partnerships in Biotech/Pharma
January 29, 1999,
Participants List

Charles Arntzen
President
BoyceThompson Institute for Plant Research

Seth Berkley
President
International AIDS Vaccine Initiative

Lincoln Chen
Executive Vice President
The Rockefeller Foundation

Somsak Chunharas
Head
National Institute of Health, Thailand

Gordon Conway
President
The Rockefeller Foundation

Joe Cook
Director
Program for Tropical Disease Research
The Edna McConnell-Clark Foundation

Atul Dhir
President
Health Strategy Advisors

Teuku Meuraxa Djoharsjah
President
PT BioFarma, Indonesia

Jurgen Drews
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John Erickson
Senior Scientist
NCI-FCRDC

Max Essex
Chairman, Department of Cancer Biology
Harvard AIDS Institute

Graham Fagg
Head of Intellectual Property
The Wellcome Trust

Sam Fiorello
Vice President
Donald Danforth Plant Science Center

William Foege
Distinguished Professor
Rollins School of Public Health
Emory University

Eloi Garcia
President
Oswaldo Cruz Foundation

Win Gutteridge
World Health Organization

Seth Harrison
General Partner
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Tamar Howson
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Alice Illchman
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Paul Klingenstein
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Joshua Lederberg
Professor Emeritus
Laboratory of Molecular Genetics & Informatics
The Rockefeller University

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Public-Private Partnerships in Biotech/Pharma

January 29, 1999, Participants List

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Center for Vaccine Development
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Managing Director
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Seung-il Shin
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Albert Siemens
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Harold Varmus
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Roy Widdus
Coordinator
Children's Vaccine Initiative/WHO

THE ROCKEFELLER FOUNDATION

January 29, 1999 Meeting on Public-Private Partnerships in Biotech/Pharma

Meeting Note

The purpose of this meeting is to discuss ways in which public sector groups can partner with biotechnology and pharmaceutical companies to accelerate the discovery, development and distribution of better health products for major infectious diseases afflicting the world's poor.

More specifically, by assembling leaders from industry, government, academia and philanthropy, this meeting attempts to answer the question: how can public-private partnerships contribute to better, faster and cheaper health products for orphan diseases?

A number of observations about the current global context and trends pertinent to the development of health products for orphan diseases underlie this initiative. These include:

- the explosion of scientific knowledge and the rapid emergence of better technologies facilitating "rational" drug design;
- a proliferation of new specialized entrants to the pharmaceutical industry (e.g. biotechnology companies, Contract Research Organizations, Contract Manufacturing Organizations, and Contract Sales Organizations);
- the importance of corporate citizenship and good will and the emergence of innovative public-private partnerships;
- increasing recognition in the public sector of the need to invest in downstream product discovery and development;
- the largest expansion of individual wealth in history creating new philanthropists.

To facilitate discussion and comprehension of the background documents it is important to clarify a number of fundamental concepts: the "health product life cycle," "public-private partnerships," and "orphan diseases."

Health Product Life Cycle

For the purposes of this meeting we identify a simplified life cycle for health products (drugs, vaccines and diagnostics) consisting of three main phases: discovery,

development and distribution.

Discovery includes the establishment of targets for therapeutic intervention, the identification of lead compounds with optimization through to proof of principle, initial safety evaluation, and product preparation.

Development refers to the conventional Phase I, II and III clinical trials and safety evaluation (toxicology, carcinogenicity). Development also entails the evolution of pharmaceutical product processes in light of the need to meet quality assurance and regulatory specifications.

Distribution includes regulatory approval (e.g. FDA, BNP), full-scale manufacturing capacity, distribution infrastructure, and product information/education to providers.

Public-Private Partnerships

Partnerships between public and private entities are *strategic alliances* for mutual gain. *Each organization commits human, financial or technical resources (or a combination)* for securing tangible and intangible benefits in line with its own mission or goal. Successful partnerships generally involve the following:

- Leadership that initiates, supports and nurtures the relationship between the entities and the establishment of mechanisms for joint coordination.
- Shared values fostering specific humanitarian and corporate citizenship goals.
- Access to resources otherwise not available because of cost, technological, marketing or institutional reasons.

Orphan Diseases

Diseases affecting large numbers of people with low purchasing power primarily living in developing countries are described as "orphan" diseases[1]. These are diseases for which the market potential of health products is considered to be so small that they do not readily attract private sector efforts for health product development. They are typically endemic infections in developing countries such as Malaria, Tuberculosis, Cholera, Shigella Dysentery, Leishmaniasis, and Trypanosomiasis etc.

[1] Other diseases with low incidence such as Myasthenia Gravis or Cystic Fibrosis might also be considered as "orphan" given the limited global market for a potential product.

Public-Private Partnerships in Biotech/Pharma Meeting
January 28-29, 1999

Gary's Group
Trustees Dining Room

Charlie Arntzen
Seth Berkley*
Gordon Conway
Joe Cook
T. Djoharsjah
Max Essex
Graham Fagg
Eloi Garcia
Josh Lederberg
Mike Levine
Josh Lewis
Paul Maddon
Lita Nelson
Bernard Pecoul
Gordon Perkin
Ron Saldarini
Gurinder Shahi
Rod Sharp
Seung-il Shin
Nigel Twose
Roy Widdus

*Group Rapporteur

Vannus

Foegl.

Conway Berkley Cuttenday Pecoul.

Lewis Widdus

Chen-Pecoul.

Themes for Discussion in the Break-out Groups
R&D on Orphan Diseases
(45 minutes for each session)

* *Common themes across sessions:*

- What are some of the constraints to product development for orphan diseases ?
- Is a single-disease focus more conducive to public-private partnerships or does a generic focus on orphan diseases provide economies of scope ?
- How to provide incentives to disseminate information on new opportunities (e.g. shelved leads and targets, library inventories) ?
- Beyond information, what will it take for public-private partnerships to happen ?
- How to take advantage of opportunities emerging from the increased segmentation in the Pharma/Biotech industry ?

1. Discovery

Ways in which public-private partnerships can:

- make more accessible the growing corpus of new scientific information relevant to discovery research;
- enable greater access for orphan disease researchers to new technologies (high throughput screening, combinatorial chemistry);
- organize directed/entrepreneurial research (research priority setting for targets and lead compounds);
- nurture capacity for health product discovery in endemic countries;
- facilitate early licensing of promising compounds or technology for application in orphan diseases.

2. Development

Ways in which public-private partnerships can:

- decrease financial barriers for promising compounds to enter development;
- facilitate entrepreneurial development (product specification; specimen banks);
- enhance clinical trials capacity to test promising compounds in endemic countries;
- upgrade and harmonize the efficiency of regulatory agencies in endemic countries;

3. Distribution

Ways in which public-private partnerships can:

- improve the assessment of market demand and segmentation in endemic countries;
- take advantage of novel technologies that transform the manufacturing and distribution of health products in endemic countries;
- create purchase funds to make demand more predictable;
- utilize informal distribution networks (e.g. of NGOs) to complement government efforts.

Conway

: simplifying clinical trials

- reexamine RCT as sacred cow.
  - as post-market surveillance.

: Tool Box. – contractual

- Tier pricing.

Overview of the Case Studies

To stimulate discussion and new ideas, we have compiled a set of case studies that demonstrate unique public-private partnerships. Not all are drawn from the health field; however, they bring important insights to both the variety and complexity of public-private partnerships for health product development. This introduction employs the three phases of the health product life cycle (discovery, development and distribution) to briefly highlight key components of the attached case studies.

Discovery

Health product discovery efforts for orphan diseases are inhibited by a number of factors. Traditional public sector funding streams support basic science research and researchers: there is little experience or demand for directed (entrepreneurial) drug discovery research emanating from the public sector. On the other hand, there has been limited private sector research investments in directed drug discovery for orphan diseases because of their relatively small market potential. The case studies point to a number of different mechanisms for stimulating discovery research for orphan diseases:

- Through the Consortium for Industrial Collaboration in Contraceptive Research (CICCR), a public sector consortium of donors and a not-for-profit organization undertakes priority setting, information dissemination and funding of early and translational research for new contraceptives in partnership with industry (Case 1).

- Bio-engineered potatoes capable of expressing antigens are being developed into edible vaccines through a partnership between an emerging biotech company, Axis Genetics, and a not-for-profit research institute, the Boyce Thompson Institute for Plant Research (Case 2).

- New vaccine technologies involving alpha virus vectors and naked DNA are being developed with HIV clades found in developing countries through "International Vaccine Development Partnerships" promoted by the International AIDS Vaccine Initiative (IAVI) (Case 3).

- To stimulate the identification of new leads and targets, the Cystic Fibrosis Foundation acquires licenses to compound libraries from combinatorial chemistry companies and negotiates access to the high throughput screening capacity of other platform technology companies (Case 4).

- The New Medicines for Malaria Venture (MMV), a public venture capital fund, seeks to finance anti-malarial drug discovery research based on explicit partnerships between academia and pharmaceutical companies (Case 5).

- By providing university researchers with access to exceptional plant diversity and new biotechnology tools from industry, the Danforth Center aims to shorten the path from discovery to practical application of sustainable food and forest products (Case 6).

Development

In general, development research on orphan diseases is constrained by a dearth of clinical trial and product development capacity in areas where orphan diseases are endemic. The limited number of existing facilities in developing countries lack sufficient coordination for multi-country trials, are expensive, and have trouble raising the requisite funds for development research. The cases identify a number of mechanisms for facilitating development research on orphan diseases:

- To encourage development of new drugs through Phase II clinical trials, the Cystic Fibrosis Foundation provides "Therapeutic Development Grants" to biotechnology companies as well as access to a network of "Therapeutic Development Centers" specialized in conducting Phase I and II clinical trials (Case 4).

- To accelerate the emergence of new diagnostics for TB, the Global TB Diagnostics Initiative, a public-private collaboration, has established pragmatic performance guidelines for new TB diagnostics, standardized protocols for their assessment and created a well-characterized global specimen bank against which new diagnostics can be tested (Case 7).

- In its attempts to catalyze HIV vaccine development research, the International AIDS Vaccine Initiative (IAVI) includes manufacturers with a pilot production facility and developing country clinical research teams based at sites with trials capacity in their "International Vaccine Development Partnerships" (Case 3).

- The New Medicines for Malaria Venture (MMV), a public venture capital fund, is creating a 'virtual' drug development unit capable of taking promising compounds through phase 2 clinical studies (Case 5).

- To catalyze the commercialization of technologies and products for orphan diseases, new contraceptives, and agricultural technology that benefits the poor and disadvantaged, the Rockefeller Foundation recently established a Program Venture Experiment (ProVenEx) to provide pre-seed and pre-venture capital funding to small and expanding companies (Case 8).

- In the field of agriculture, the International Service for the Acquisition of Agri-Biotech Applications (ISAAA), a public-private partnership, facilitates the accessibility of proven bio-technologies to developing country researchers for application to agricultural production challenges related to yields, pests and health of food crops (Case 9).

Distribution

Many countries where orphan diseases are endemic lack acceptable manufacturing standards, especially for products such as vaccines. They also lack an adequate and coordinated health product distribution infrastructure. Efficacious products are often inaccessible due to their high price. Efforts to make products affordable through differential pricing agreements have in some cases led to seepage of the low priced products back to high priced markets. Private industry is also cautious about distributing their products in many countries due to a history of different standards in intellectual property rights and the market threat represented by generic manufacturers.

- Merck's corporate contributions of Ivermectin to treat millions at risk of blindness have been facilitated through a complex but highly efficient drug distribution partnership (Case 10).

- The International Trachoma Initiative, a partnership involving Pfizer and the Edna McConnell Clark Foundation, plans to distribute the antibiotic Azithromycin in five countries in an effort to eliminate blinding trachoma (Case 11).

- Intellectual property rights agreements have been negotiated for HIV vaccine technologies in development such that if the vaccine producer is not inclined to distribute vaccines in endemic countries, IAVI has the right to license the technology to other manufacturers (Case 3).

- Several partnerships facilitated by IAVI are exploring mechanisms for ensuring access to new products through publicly funded or corporately subsidized product purchase funds (Case 3).

CASE STUDIES

Consortium for Industrial Collaboration in Contraceptive Research

Background

The Consortium for Industrial Collaboration in Contraceptive Research (CICCR) was established in 1995 by CONRAD with funding from the Rockefeller, Andrew W. Mellon, William and Flora Hewlett Foundations, and others. CONRAD is a not-for-profit organization which supports the development of better, safer and more acceptable methods of fertility regulation suitable for use in developing countries.

CICCR funds promising leads under investigation by not-for-profit organizations in developed and developing countries in the following three areas of research:

- Contraceptive methods for men;
- Vaginal methods that prevent conception and the transmission of sexually-transmitted diseases (STDs); and
- Monthly contraceptive regimens, which could be post-coital, anti-implantation, or menses-inducers.

Problem Being Addressed and Strategy

CICCR's primary goal is to stimulate industry's commitment to developing new contraceptives and anti-microbial products for sexually transmitted diseases. Innovation in the contraceptive and anti-STD area has been hampered by 1) a lengthy and costly research and development process and 2) perceptions among pharmaceutical and biotechnology companies of multiple barriers and limited market potential for new contraceptive products.

To stimulate research and development in new contraceptive and anti-STD technologies, CICCR provides funds to researchers in developed and developing countries through three different funding mechanisms:

1) Early research and discovery: CICCR's "feasibility projects" program supports innovative, high-risk research in the three areas outlined above. Funding from this program is intended to:

   i) support interdisciplinary research,
   ii) mobilize intellectual capacity outside the field,
   iii) recruit new investigators into the field, and
   iv) help bring early research and discovery projects to the stage where an industrial partner may become interested in collaborating on further development.

2) Preclinical and early clinical development: CICCR provides matching funds to promote collaborations between not-for-profit research institutions and pharmaceutical/biotechnology companies to develop products through Phase II clinical trials. CICCR also provides funding to public-private partners to explore the feasibility of commercial development of scientific findings from these trials, obtain patent protection for their invention, and seek out new industrial collaborations.

3) Developing country collaborations: Twinning funds are provided by the Andrew W. Mellon Foundation for collaborations between Mellon-supported Reproductive Biology Centers in the U.S. and twinning centers in developing countries.

Progress to Date

To date, CICCR has funded 13 early research and discovery projects and 18 awards on 10 leads in the preclinical and early clinical development projects area with matching funds from industry. CICCR funds go to non-profit research institutions. Of these, the most advanced projects include two high molecular weight sulfated polymers and a promising delivery technology which are being co-developed with industrial partners and have demonstrated in vitro anti-HIV, anti-HSV, and antigonococcal activity, and promising anti-fertility activity in rabbit models. Three projects are within six months of Phase I clinical trials.

Lessons Learned

- Preclinical and clinical development of new products takes time and considerable attention and coordination between both public and private partners. It has taken approximately 4-5 years for a new compound to be ready for Phase I clinical trials.

- In order to accelerate the development of contraceptive and anti-STD products, private partners which have resources and management dedicated to this product line are required.

Prepared by Jackie Khor, The Rockefeller Foundation
with assistance from Henry Gabelnick, Director of CONRAD

The Boyce Thompson Institute for Plant Research

The Boyce Thompson Institute for Plant Research, Inc. (BTI) is a not-for-profit entity which was incorporated in the State of New York in 1924. The impetus to establish the institute was Mr. Thompson's observation of starvation in Russia and Poland at the end of World War I when he led Red Cross relief efforts in those areas. After his return to the US, he created an endowment of over $10 Million in 1924 to support an institute which would "conduct research on plants for the benefit of mankind." This endowment has grown to the current level of $70 Million; annual withdrawals support the core BTI scientist's salaries, institute infrastructure costs, and some research funding.

BTI is located on the campus of Cornell University in a building provided by the State of New York. An affiliation agreement with Cornell allows access to the University libraries and other resources, and creates a means for BTI researchers to participate in University graduate instruction and to serve as graduate student advisors. Institute scientists compete for grants and contracts to cover costs of most research conducted in the Institute. Government agencies are the largest source of research funds, with NSF and NIH being the agencies which provide the largest segment of these grants.

To improve financial stability and expand its research capabilities, the BTI solicits research support from Foundations and Industry. Scientists are encouraged to apply for industrial grants and contracts if the research to be conducted is exploratory and is not product development. At present, about 25% of the institute's research funding is from Industrial sources. All intellectual property agreements with corporations are made by the management team of the BTI, lead by a Vice President for External Affairs (Joyce Frank). While the BTI president has designated authority to enter into industrial agreements, it is customary to discuss all large agreements with some or all members of the institute's Board of Directors.

Partnership with Axis Genetics, PLC:

The largest current single industrial research grant to the BTI is from Axis Genetics, PLC (Axis). These funds are a component of a licensing agreement which was established in June, 1998. The agreement gives Axis an exclusive right to commercialize all BTI technology in the field of "human subunit vaccines produced in transgenic plants." The exclusive license is contingent upon Axis' fulfillment of three obligations: 1.) granting to the BTI of Axis stock equal to 15% of the outstanding Axis stock at the time of the dispersement (completed in June, 1998); 2.) payment of a total of $3.0 Million to the BTI as a licensing fee, with payments made in 1999 and 2000 (on-going); and 3.) a research grant of $3.0 Million paid over three years beginning on June 1, 1998 (underway).

Subject of the Axis-BTI Partnership:

The broad goal of the Axis-BTI partnership is to develop technology for the creation and production of "Edible Vaccines" (EV). This strategy was pioneered by BTI scientists over the last eight years. The central concept is that transgenic plants can be constructed which express immunogenic proteins, where such proteins are virulence or colonization factors of pathogenic bacteria, viruses or parasites. A component of the strategy is that the proteins are caused to accumulate in edible plant tissues in forms that will cause them to be orally immunogenic if the plant tissues are consumed as food. The research was extended to human clinical trials early in 1998; the successful outcome verified the utility of plants as a production and delivery system for oral "subunit" vaccines.

Research by Axis, since it founding in the mid-90s, had focused upon the use of plant viruses as a means to drive protein expression in plants. One component of their efforts was the production of candidate vaccines.
With the implimentation of the Axis-BTI partnership, the company has made a transition to a primary focus on transgenic plants for product delivery, and human vaccines as its exclusive interest. The partnership's technology development has become a key component of the corporate activities.

Unique Features of the Partnership:

The partnership meets two major tactical goals of the BTI. First, it potentially will enhance the endowment of the institute by growth in value of the Axis equity received (which is held as part of the BTI endowment resources, but has a two year restriction on sale). Secondly, it enhances our research capacity by providing on-going direct cost support to augment government grants. In addition, it (hopefully) will help achieve the Institute's long term strategic goal of providing technology for the benefit of mankind by assuring that corporate efforts will make novel vaccines widely available.

With respect to research, the Axis partnership was designed to encourage a shared-planning, collaborative research effort. The company has exclusive rights to any technology "in the field" which the institute owned at the time of the agreement signing (June, 1998) and to any development arising in the institute during the course of research funding by Axis. This avoids piece-meal licensing of individual patents or patent applications. It also gave Axis immediate access to all biological reagents which existed in the BTI, including plant transformation vectors and prototype plant material.

A significant part of the research conducted in the BTI on plant-based vaccines is supported by grants from government agencies (especially NIH). In addition, Foundations have supported some vaccine projects. (This includes the Rockefeller Foundation, which has supported the training of scientists from developing countries.) The intellectual property of this research is obligated to Axis by BTI, except as restricted by federal or other constrains. This gives Axis a "guarantee" of early access to new technology that can have an impact on their business.

How the Partnership Operates:

To ensure that the company and BTI meet shared goals, the contract between them has defined a Project Management Committee (PMC) with two members from each side. This committee meets quarterly to discuss projects and agree upon the work to be conducted. If the committee can not agree, the conflict is resolved by the CEOs of the respective organizations. If no agreement can be achieved by the CEOs, the contact reverts to a non-exclusive for Axis, and further payments by Axis to BTI can be terminated (although the Axis stock held by BTI is not returned). The incentive is for Axis to negotiate to reach consensus to ensure its continued exclusive rights to BTI technology, and for BTI to negotiate for the same consensus to ensure continued research funding and improved value of its corporate equity. To implement the PMC decisions, the BTI has recruited a Project Manager whose sole function is to serve as a liaison with Axis scientists and management; this individual also acts as an intellectual property liaison with the Axis patent attorney responsible for protection of the BTI-derived technology.

The research conducted by the BTI, which is funded by Axis, is designed by the PMC, and defined by the contract, to be in support of studies which will advance basic discoveries to human clinical trials. This serves both the BTI (which would like to achieve a benefit to mankind, which requires that the edible vaccine technology be moved to practical use) and Axis (which needs clinical testing as a step to product introduction). It also serves to ensure that the mechnanism-focused research, which is funded by agencies such as NIH, are not left simply as publications in peer-reviewed journals. The Axis funding encourages efforts (which a grant panel may consider irrelevant) such as transformation of a difficult experimental plant species because it has very desirable commercial production traits. Both BTI and Axis benefit from this, since the extra time spent in creating a commercially useful cultivar has the long term benefit of allowing much more detailed large scale pre-clinical or clinical studies in the future. This work could simply not be justified on a three year government grant.

One feature of the Axis-BTI agreement was added to ensure that the BTI mission is achieved; a section of the contract was included to allow the BTI to utilize it's technology to introduce vaccines into developing countries if Axis did not have a corporate plan to enter that market. To date, the use of this clause has not been developed.

Summary of the Axis-BTI partnership:

We are just past the mid-point of the first year of this partnership. The PMC is functioning with ease, and three commercial targets have been identified based upon prior research by the BTI. A second human clinical trial is about to start, which is facilitated partially by the Axis agreement. A third human clinical trial is planned later in 1999; this is for an oral Hepatitis B vaccine. Axis support has been and will be critical to

this effort, since we need comparatively large amounts of a commercially usable plant cultivar to finish the pre-clinical testing to ensure timely human trials.

Axis' business planning has consistently visualized the US and European vaccines markets as the largest and most profitable to enter. At the same time, they recognize that the "edible vaccine" approach has unique utility in making products that could be cost-effective in the developing world. It is likely that the Axis-BTI partnership can enhance the "third world" opportunity through collaborations with scientists in developing countries.

Prepared by Charles J. Arntzen, Boyce Thompson Institute

The International AIDS Vaccine Initiative

The International AIDS Vaccine Initiative (IAVI) was established as an international non-governmental scientific organization in 1996 because of the perception that the HIV vaccine effort was lagging. Its mission is to ensure the development of safe, effective, accessible preventive HIV vaccines for use throughout the world. It has a small secretariat in New York with partner organizations in the United Kingdom, France and South Africa and consultants working throughout the world. It also works closely in partnership with UNAIDS, the World Bank, the vaccine industry and other authorities. It is the Collaborating Center for HIV Vaccine Development of UNAIDS.

Strategies:

(1) Global Communication, Education and Advocacy to ensure that HIV vaccines are high priority and receiving the necessary world-wide effort to guaranty their development;
(2) An aggressive applied Scientific Vaccine Development Program that focuses on launching the development of promising vaccines appropriate for use in developing countries; and
(3) Creating an Enabling Environment for industrial participation by providing adequate incentives (a commercially viable market, R&D subsidization, trial and regulatory simplification, etc.) for industry to fully participate in HIV vaccine development.

A distinguished scientific advisory committee composed of 12 vaccine developers and scientists from 9 countries oversees the science program. To accelerate vaccine development, IAVI created the concept of International Vaccine Development Partnerships. Each Partnership includes researchers with a promising vaccine candidate, vaccine manufacturers with a pilot production facility and clinical researchers at an appropriate vaccine test site. Vaccines are specifically designed for the countries in which they will be tested to assure as close as possible match of the virus with the vaccine strain. At the end of 1998, the first two Vaccine Development Partnerships have been launched bringing together scientists, vaccine manufacturers and researchers from the US, Europe and Africa. The first will create a clade (subtype) C vaccine made from a South African strain based upon Venezuelan Equine Encephalitis alphavirus replicon particles. This is based on a partnership between AlphaVax, a small US Biotechnology Company, and South African researchers. The second will produce an HIV vaccine that combines two separate vaccine constructs: a naked DNA vaccine, plus a modified vaccinia Ankara (MVA) virus vaccine both derived from Clade A strains of the virus circulating in Kenya. This partnership includes Oxford University and the Medical Research Council of the United Kingdom, Impfstoffwerk Dessau-Tornau,GmbH (IDT), a pharmaceutical company in Roßlau, Germany, which produces the MVA-HIV construct, and scientists at the University of Nairobi who will be testing the vaccines. As resources permit, over the next few years, further product development teams will be launched.

The current global pattern of vaccine development is to create a vaccine for the industrialized world, price it high and amortize the R&D costs over a short period. There is no explicit strategy for vaccine development for non-industrialized countries. IAVI's goal is to change the current paradigm of vaccine development so that AIDS vaccines will be launched and available simultaneously in the North and South. To ensure accessibility of a future vaccine to populations in greatest need, IAVI has negotiated innovative intellectual property agreements that combine the best mechanisms of the for-profit and not-for-profit sectors. If the producer does not want to meet production requirements under these cost constraints for the developing world, IAVI has the right to provide the vaccine technology to another manufacturer.

IAVI is also working on vaccine production capability to assist in the creation of national vaccine programs that have commercial manufacturing capacity. Programs have thus far been established in China, India and South Africa. IAVI is also working closely with the World Bank through a newly created Bank-wide Task Force on New Instruments to Promote R&D for an AIDS Vaccine for Developing Countries. Through this mechanism, IAVI is exploring the current barriers to industrial participation, the commercial market for products, as well as potential new instruments for financing development or availability of an HIV vaccine.

Outcomes

In the three years that IAVI has existed, it has been instrumental in getting the issue of HIV vaccines back on the public agenda; doubling the global resources dedicated to HIV vaccine development; launching promising vaccine approaches designed specifically for the developing world; and creating innovative social venture capital approaches to finance HIV vaccine development. It has operated with some characteristics of a virtual pharmaceutical company, a social venture capital fund, a policy think tank, and an advocacy group. It has operated between the public and private sectors, between developed and developing countries and between governments, non-governmental organizations and UN agencies. This new model has a number of lessons which can be useful for other product development initiatives.

Lessons Learned

Initially, many felt that the challenge of HIV vaccine development was too difficult and too costly for a not-for-profit to have a major effect. This has turned out to be false. The combination of 1) a laser-like focus; 2) including and catalyzing the different sectors who should work in this area (industry, government, activists, consumers); 3) building the initiative on a platform of the best science and aggressively funding in this area to create model programs; 4) using the tools of both the for-profit and not-for-profit sectors; and 5) providing sustained and impassioned leadership to build a web of global influentials have all contributed to a visible global effect of this effort in its short three years of operation.

Dr. Seth Berkley, President, The International AIDS Vaccine Initiative

The Cystic Fibrosis Foundation

Cystic Fibrosis (CF) is a complex disease caused by genetic mutations that affects approximately 30,000 individuals in the U.S. Currently, there are no known cures for CF. Acute and chronic respiratory infections and ensuing pulmonary complications are directly responsible for the death of more than 90% of CF patients. Treatments include chest percussion, postural drainage, antibiotics to control chronic respiratory infections, and pancreatic enzyme therapy to alleviate the nutritional complications of the disease.

CF is a disease with some similar market characteristics to those of infectious diseases that largely afflict developing countries, among which is that the estimated market size of approximately $200-$300 million per year for CF drugs is relatively small by pharmaceutical industry standards. Two of the major drugs used to treat CF – Pulmozyme and TOBI™ – have annual sales of $80 million and $60 million respectively.

In order to accelerate the development of drug treatments for CF, the Cystic Fibrosis Foundation (CFF) has developed partnerships with research institutions and biotechnology companies. In the case of TOBI™, the research and development work through Phase II and to the beginning of Phase III clinical trials had been conducted by the University of Washington. The drug was then commercialized and is being marketed by PathoGenesis Corporation.

CFF's Public-Private Partnership Strategy

Partnerships for New Compound Discovery. In order to prime the pipeline for new drugs, the CFF licenses compound libraries from combinatorial chemistry companies and works with other companies which have high throughput screening capabilities to identify new lead compounds. If a promising lead compound is generated, the CFF and combinatorial chemistry company will partner with a biotechnology company to commercialize the product.

Clinical Development Partnerships. The CFF establishes partnerships with biotechnology companies through its Therapeutics Development Grants, which provides funds to businesses that will develop commercial products. Under this program, the CFF provides up to $1.7 million over two years in matching funds to biotechnology companies for developing a product through Phase II clinical trials.

Successful products after Phase II are then developed by the biotechnology partner. If a product is approved by the FDA, the biotechnology partner returns to CFF the latter's matching funds. In addition, the CFF receives royalty payments of 1% of net sales for the life of the patent. To avoid potential conflicts of interest, the CFF will at times sell its royalty rights.

The CFF's biotechnology partnerships are milestone-driven and reviewed regularly by a peer advisory group. The biotechnology partners have the opportunity to use the CFF's specialized network of Therapeutic Development Centers. These centers conduct Phase I and II clinical studies of novel therapies in CF and have access to approximately 20,000 cases of CF in the US.

In addition to funding partnerships with biotechnology companies in the lead identification and clinical development phases, the CFF provides competitive awards for 1) research related to CF at the early pilot, feasibility and research phases, 2) training clinical investigators, physicians and scientists, 3) complementing NIH funds, and 4) expanding its Therapeutic Development (clinical trial) centers.

250,000 volunteers, working through the Foundation's 65 chapters and branch offices, support CFF research, medical care, public policy and education programs and fund-raising. The Foundation depends on public support for its funds.

Outcome

Over the past ten years, the CFF has funded eight products through the clinical development phase. These products are in various phases of development, with one approved (TOBI™).

Lessons Learned

The CFF's biotechnology partnership strategy requires it to be knowledgeable about and develop relationships with biotechnology, combinatorial chemistry, contract research, and other health products services companies that could play a role in the CF drug niche. The CFF is also very actively involved in these partnerships by helping its company partners connect to clinical trial centers, research institutions, and other resources required to develop and commercialize a CF drug.

Prepared by Jackie Khor, The Rockefeller Foundation (after consulting with Dr. Robert Beall, President of The Cystic Fibrosis Foundation

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NEW MEDICINES FOR MALARIA VENTURE (MMV)

Proposal to Establish a Public/Private Sector Partnership to Foster the Discovery and Development of New Antimalarial Drugs

OUTLINE PROPOSAL AND STATUS AT 15 JANUARY 1999

1. Introduction

The infectious disease burden inflicted on the developing world by tropical diseases continues to exact a huge price both in human suffering and in contributing to poverty and underdevelopment. The case of malaria is particularly acute. Because of scientific and technical obstacles vaccines are non-existent and, due to the growth of resistance, drugs are becoming inadequate. New products are desperately needed, especially affordable drugs to treat uncomplicated disease. However, the increased costs of developing and registering pharmaceutical products, coupled with the prospect of inadequate commercial returns, has resulted in the withdrawal of the majority of research-based pharmaceutical companies from R&D investment in tropical diseases, especially from discovery research activities. The public sector has maintained basic science funding, but in general lacks the expertise, mechanisms and resources to discover, develop, register and commercialise new products. If the status quo continues, the outlook for the control of many of the world's major diseases, as we approach the new millennium, looks bleak.

This document formulates a proposal, primarily in the context of malaria, to address these issues. It is the result of discussions during 1997/8 in a Strategic Planning Group composed of public sector and private sector representatives[1]. These discussions revealed that for a proposal in this therapeutic area to be attractive to the public sector, it was essential that it included pharma industry participation to allow access to critical knowledge and experience of product discovery and development and to key new technologies such as combinatorial chemistry and high throughput screening. It was also essential that it be integratable into or complementary with existing malaria initiatives, such the Roll Back Malaria (RBM) programme and the Multilateral Initiative for Malaria in Africa (MIM). For the private sector, there was a desire to help, but also a need to ensure that there was no risk of setting a precedent for other therapeutic areas and that any scheme proposed had a competitive element and a flexible exit mechanism. There was a willingness to contribute access to the new technologies as gifts-in-kind, but also a feeling, since this was a public health issue, that finance should come primarily from the public sector. Both public and private sector representatives also felt that it was highly desirable that mechanisms be developed by the public sector to subsidise (antimalarial) drug purchases for poor populations, since this would facilitate the commercialisation of new antimalarial drugs and enable any antimalarial R&D activity to become partially self-financing.

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[1] Harvey Bale Jr. (IFPMA); Amie Batson (World Bank); Louis Currat (Global Forum for Health Research); Tim Evans (Rockefeller Foundation); Richard Feachem (World Bank); Tore Godal (WHO/TDR); Win Gutteridge (WHO/TDR); Bob Howells (Wellcome Trust); Trevor Jones (ABPI); Rob Ridley (Hoffmann-La Roche); Simon Sargent (Glaxo Wellcome); Marcel Tanner (SDC).

2. Proposal

It is proposed that the public and private sectors jointly establish an organisation to foster and resource the discovery and development of new antimalarial drugs. This **New Medicines for Malaria Venture (MMV)** would create a 'public venture capital fund' to solicit and resource on a competitive basis drug discovery projects built on partnerships between public sector (mainly academic institutions) and private sector (mainly pharmaceutical industry) institutions. This should result in a portfolio of properly funded and adequately manned projects on par with industry-run discovery projects. It is anticipated that most of these projects would be housed in academic institutions, but some may be pharma company-based. The most promising development candidates discovered as a result of these projects would be fed into a 'virtual' drug development unit, financed and administered by the MMV and capable of taking compounds through to registration. This stage of the process would also contain competitive elements, both with respect to projects attaining and maintaining a position in the development portfolio and by contracting development in such a way that the process was competitive by industry standards. At the appropriate stage during such development (usually after Phase 2 clinical studies), the MMV would seek industrial partners for the commercialisation of products at appropriate prices. Such partners might be either large or small pharma companies. The goal of the MMV, once fully developed, would be to secure the production on average of one registered new antimalarial drug every 5 years.

To be fully effective resources of around **$15 M p.a. would be needed initially** to establish a series of drug discovery research projects, **rising to around $30 M p.a.** over three to five years as these projects started to produce candidates for drug development.

3. Organisation

The proposed MMV would be made up of 2 elements: a **'public venture capital fund'** of cash and other necessary resources; and a small **management team** to advocate, foster, coordinate and resource research and development appropriate to the registration of new antimalarials, and to administer and manage the fund.

3.1. Fund

- The fund would consist of cash, plus gifts-in-kind appropriate to antimalarial drug discovery and development.
- **The cash would come primarily from governmental agencies and philanthropic institutions**, on a non-reimbursable basis, though private sector funds would also be welcomed.
- **The gifts-in-kind would come primarily from the private sector** (eg access to combinatorial libraries and high throughput screening systems), but could also come from the public sector (eg access to primate models of human malaria).

- The fund managers and their advisers would finance drug discovery research proposals (up to $ 3.5 M p.a.) on a **competitive basis**, consistent with the goal of generating development proposals for candidate antimalarials.
- Funding for individual projects could be raised, lowered or terminated depending on a project's progress and the status of other projects in the fund's portfolio.
- The fund managers and their advisers would **independently** select and finance the development of the most promising of the candidate antimalarials discovered and at an appropriate stage outlicense their manufacture/commercialisation to an industrial partner.
- Downstream revenue accruing from out-licensing would be reinvested in the fund.

3.2. Management Team

- This would consist of a Director and a small management team of about 8 people in total.
- The Director would be appointed by and answerable to a **Board** consisting of representatives of the institutions resourcing the MMV (ie public sector and industry donors of cash and/or gifts-in-kind).
- An expert scientific advisory committee would be appointed both to advise the management team and the Board.
- **The operational paradigms of the MMV would be those of industrial management of a R&D portfolio and not those of a public sector science funding agency.**
- The main tasks of the management team would be:

  a) to work closely with appropriate academic institutions and private sector companies to encourage and facilitate the putting together of discovery research proposals, their reviewing and funding, the assessment of their progress and their evolution, if appropriate, into a development proposal;

  b) to identify a third party or to set up and administer a 'virtual' development operation to manage the development process;

  c) to ensure a scientifically balanced portfolio of discovery and development projects;

  d) to negotiate appropriate contracts with public and private sector partners;

  e) to facilitate production and commercialisation of products arising from successful development projects;

  f) to optimise appropriate financial return to the MMV fund from commercialised products;

  g) to raise funds and to access other resources (eg gifts-in-kind); to administer the operation of the Board and the expert scientific advisory committee;

  h) to work closely with public sector agencies and companies with an interest in tropical disease R&D and tropical disease control.

4. Modus operandi of R&D

4.1. Discovery

- This would be done through MMV's fund resourcing discovery research proposals on a competitive basis. The start point would normally be a validated biological target, but not necessarily with an associated chemical lead.
- The proposals would result from partnerships established between academic centres, pharmaceutical companies and MMV and would be built on agreements safeguarding their respective interests, including IPR.
- Partner companies would contribute gifts-in-kind (most importantly, know-how of and expertise in the drug discovery process, access to chemical libraries and high throughput screening and data handling systems), but the level of their cash contribution would remain open and there would be no downstream obligations.
- A commitment of gifts-in-kind would also be expected from the partner academic institutions, where the work would be carried out in most cases (eg laboratory space and scientific and administrative infrastructure).
- These partnerships, if successful, would most likely interact later with the MMV's virtual drug development unit, but could seek their own development paths.

4.2. Development

- The MMV would obtain access to, or would set up, a 'virtual drug development unit' capable of taking compounds through from early pre-clinical development to registration.
- This unit would contract its work packages out on a competitive basis.
- WHO/TDR have established such a unit and could take on this responsibility, at least initially. They could also act as a repository of expertise if it was later decided to support other foci for development.
- Development projects, at least for Phase 3 clinical studies onwards, would be carried out with a private sector partner, based on an agreement specifying the financial arrangement between the MMV and the partner and covering their respective financial contributions and the split of potential profits and losses.
- The development projects selected and the agreements under which they are carried out would be negotiated with particular regard to optimising the chances of affordable, cost-effective products for the treatment of malaria. Within this framework, attempts would be made to optimise returns to both the MMV and its commercial partners[2].

[2] To facilitate the affordability and cost-effectiveness of new drugs and to optimise such returns, discussions are currently in progress between interested public sector agencies to explore the possibility of public subsidising of drug purchases in poor populations.

5. Current Status of MMV

- MMV has the blessing of IFPMA Council and related Groups (eg Hever) and sufficient companies are identified for the first round of discovery research proposals to be developed.
- It was endorsed by both sides at the joint WHO/IFPMA round table consultation, held in Geneva on 21 October 1998, with Dr Gro Harlem Brundtland and Sir Richard Sykes in the chair.
- The major agencies participating in MIM regard it as complementary to their activities.
- It has been accepted by WHO as being compatible with RBM and is being incorporated under the RBM umbrella and partially financed by it.
- MMV is operating initially from WHO/TDR, with its own budget lines for operations and operational support.
- Its long term location/legal status are under discussion with WHO, in order to determine if the independence necessary for its operation as a business unit are compatible with the Organization's charter.
- A short term professional is in post in WHO TDR to help administer the initiative; an Acting Director will be appointed shortly; the Rockefeller Foundation has pledged funds for a business consultant to assist the latter in developing MMV's business plan, if required; the post of Director will be advertised during 2/3Q99.
- Communication and resource mobilisation strategies are being developed. A Geneva based, independent consultant has been identified to advise on communication and communication materials. The Strategic Planning Group is being strengthened by recruitment of some new members with resource mobilisation skills. A presentation of MMV to the World Bank and other interested North American-based parties is being planned for late February 1999.
- Sufficient resources were pledged at a similar meeting held at the Rockefeller Foundation in September 1998 to fund one or two research proposals in 1999.
- A call for letters of interest for these was made in the scientific press and through the net during December 1998 and January 1999, with a deadline of 26 February 1999.
- This has already attracted a lot of interest from academic and industrial groups, suggesting that some strong proposals will be submitted.
- Plans for filtering the letters of interest and reviewing and making decisions on the proposals of those short-listed are well advanced, including the establishment of the expert scientific advisory committee.

Dr. Win Gutteridge, World Health Organization

The Donald Danforth Plant Science Center

Introduction

The St. Louis-based Danforth Foundation has joined with the State of Missouri and five partners in the Midwestern United States to form the Donald Danforth Plant Science Center. The independent, not-for-profit Danforth Center, located in St. Louis, Missouri, is designed to be the centerpiece of an innovative initiative that will apply the most modern scientific and business thinking to the age-old problem of providing food, plant and forestry products to the people of the world - - doing so in ways that can be sustained for generations to come.

The Danforth Center's founding partners are all recognized leaders in the plant sciences: the Missouri Botanical Garden of St. Louis, home to an extensive plant bio-diversity program; the University of Missouri - Columbia, Purdue University and the University of Illinois Urbana - Champaign, three leading schools with strong agricultural research traditions; Washington University in St. Louis, with one of the world's most extensive research programs in the biological sciences and genomics; and the St. Louis-based Monsanto Company, one of the world's leading life sciences companies.

Overview

One of the most important developments of the 20th Century has been the enormous increase in agricultural productivity. This increase has been made possible by developing genetically improved crops (such as hybrid corn) and cultivating them better (using irrigation, fertilization, and pesticides) to achieve maximum yield. These modern agricultural techniques have made it possible to feed the world's rapidly growing population, which has increased four-fold in the last century. Such advances did not happen by chance, but rather were built on an infrastructure of research, education, extension, production and application made possible by a farsighted collaboration of government, academia, and private industry.

The challenge that we now face is to find ways to sustain continuing increases in crop productivity to feed and improve the nutrition of even greater numbers of people in the 21st Century. Faced with these opportunities and challenges, the Danforth Center's founding partners have committed themselves to making their region and the Center an international leader in plant science and agriculture.

Mission of the Danforth Center

The Danforth Center will contribute to human nutrition and health and global sustainability in agriculture by:

- using innovative science to increase our understanding of basic plant biology and applying the knowledge gained to sustainable productivity in agriculture, forestry, and allied fields;

- promoting the practical application of new knowledge by facilitating the rapid development and commercialization of technologies and products that promise to be useful; and by,
- contributing to the education and training of graduate and postdoctoral students, scientists, and technicians from around the world.

Innovation & Application

- The Danforth Center will facilitate world-class, interdisciplinary plant research in areas including genetics, cell biology, biochemistry, and computational and structural biology.
- The Center expects its faculty will apply new discoveries to agricultural biotechnology in a manner that will shorten the path from discovery to practical application.

Education & Outreach

- Postdoctoral and graduate students from Washington University in St. Louis, the University of Missouri - Columbia, the University of Illinois Urbana - Champaign, Purdue University and other institutions will be integral components in the research of the Center. They will enrich the intellectual life and strengthen the overall capabilities of the Danforth Center.
- Scientists, advanced students, and trainees from developing countries around the world will be invited to conduct research and participate in training programs in a formal laboratory program, "The International Center for Tropical Agricultural Biotechnology (ICTAB)". Funding for such activities will include sponsorships by corporations, foundations and other international organizations.

People

- The Danforth Center's staff will be headed by its founding president, Dr. Roger N. Beachy, and 15 principal investigators who will lead multi-disciplinary laboratory projects, setting their own research agendas through consensus with the director.
- Laboratories will be composed of visiting scholars, technicians, post-doctoral and graduate students and will be equipped with state-of-the-art laboratory equipment.
- The center will eventually house 200 permanent staff and visiting scientists from partner institutions and other national and international research institutes; scientists will be attracted by the opportunity to interact with individuals doing research in different aspects of biological organization (molecular, cellular, and organismal), and with scientists who move ideas from fundamental research to commercial realization.

Sam Fiorello, Vice President, Donald Danforth Plant Science Center

The Global Tuberculosis Diagnostic Initiative

One third of the cases of TB globally go unrecognized, magnifying the pandemic and its associated mortality. Yet this diagnostic test, which was developed nearly a century ago, lacks sensitivity (high false negatives), is labor (and training) intensive, and requires good, functioning equipment and reagents. The diagnosis and treatment of acid-fast bacilli [AFB] microscopy positive [i.e. smear positive] cases of pulmonary TB is the foundation of the World Health Organization's [WHO] Directly Observed Treatment, Short Course [DOTS] strategy to control TB.

As a result of the limitations of smear-microscopy, cases of smear-positive TB [i.e. the most infectious] are often undetected. This must add to the significant number of false negatives. New diagnostics are therefore needed to facilitate and improve the detection of both smear positive and smear negative cases of TB.

In Malawi, it costs $0.31 to prepare and examine a single AFB-slide, and nine suspects are examined for each case diagnosed. Thus 27 slides must be examined at a total cost of US$8.31 to diagnose one case. WHO estimates over 7 million cases of TB worldwide each year, making the market for TB diagnostics potentially in the region of $60 million.

On the other hand, sufficient scientific knowledge and technology exists for a new TB diagnostic test. There are indeed a number of companies with serological tests based on the use of mycobacterial antigens that have been highly purified or cloned. The recent sequencing of the entire *M. tuberculosis* genome will further boost diagnostic opportunities.

Strategy: work in progress

- *Formulation of the TB Diagnostics Initiative.* During 1996, the Global TB Program at WHO reviewed the R&D arena of diagnostic tests for TB and concluded that a specific TB Diagnostics Initiative was needed to speed industrial development of the new products for use in low-income countries.
- *Building consensus.* A workshop held in July 1997 in Cleveland, OH, with participation of industry, academia and government, provided a forum to shape the initiative into a global partnership.
- *The goal of the TB Diagnostics Initiative* is to facilitate the development, approval, and employment of new diagnostics for TB in low-income countries in the next decade. The WHO-led initiative will provide a framework for interested parties to facilitate this goal [including basic and clinical researchers, the diagnostics industry, regulatory agencies, and national and local health officials] WHO will assist industry in the preparation of appropriate trial protocols and in the identification of appropriate sites for these trials.

Progress thus far

A. *Industry survey.* The initial strategy of the TB Diagnostics Initiative focused on industry. Currently, more that 50 companies have been identified with an active interest in new TB diagnostics. These companies are located in 18 countries, scattered across five continents. Visits by WHO officers to industry decision-makers have promoted potential alliances and partnerships. 50 diagnostic tests are currently under development or already in the market.

B. *Product performance guidelines.* The primary obstacle identified by industry was a lack of understanding of what products were most needed and how these products would be used in the field. The workshop in 1997 established guidelines to assist in the development of new products that would be both practical to develop and useful in the field - rather than 'ideal' - and that would still offer a profit margin for industry.

C. *New diagnostics: summary of needs and characteristics.* Together with Dr. Richard O'Brien of the CDC (USA), WHO prepared a document that describes the needs for and characteristics of new diagnostics for TB. The purpose of the manuscript is to assist industry decision-makers in their preparation of business plans.

D. *Specimen bank.* No reliable source of well-characterized clinical specimens currently exists for this purpose and the availability of such materials would greatly assist industry in developing new products. The performance of a new product using well-characterized specimens could also assist the approval process and promote the comparison of new and existing products.
A specimen bank for tuberculosis has been established through a private contractor in Boston, MA. WHO will fund patient enrollment and specimen collection in Africa and other regions to be selected. Samples will be available for a small fee to commercial and academic researchers.

Lessons learned

1. There are sufficient scientific and technological resources to develop a better diagnostic test for TB.

2. The market imperatives of industry need to be taken into account for effective product-development partnerships.

3. General product specifications by government and experts facilitates and focuses the work of private industry.

4. Specimen banks have the potential to accelerate the development and standardized testing of new products.

Prepared by Ariel Pablos-Mendez, The Rockefeller Foundation.

The Rockefeller Foundation Program Venture Experiment (ProVenEx)

Background

The goal of the Rockefeller Foundation's Program Venture Experiment ("ProVenEx") is to accelerate the development and commercialization of new technologies and products which further the Foundation's charitable interests by investing in start-up and expanding companies working in these areas of interest. The Foundation's charitable interests cover the following areas and focus on the poor and excluded:

- Technologies and products to promote ecologically-sound agricultural development.
- Research and development in reproductive health, including contraceptive products and products to prevent the spread of sexually-transmitted diseases in developing countries.
- Renewable energy.
- Employment opportunities for disadvantaged inner-city residents in the US.
- Improving learning outcomes for disadvantaged and low-income inner city children.
- Vaccines and drugs for developing country applications.

The ProVenEx Strategy

The ProVenEx strategy is based on applying venture capital investment expertise to provide financial resources and value-added business assistance to for-profit business enterprises which further the Foundation's charitable interests. ProVenEx will invest in private ventures at the pre-venture capital start-up, early and expansion stages of investment that:

1) Further one or more of the philanthropic interests outlined above, and
2) Are viable investment opportunities.

Progress Thus Far

Since March 1998, ProVenEx has been working with E.M. Warburg, Pincus & Co., LLC on identifying and evaluating potential investment opportunities. After reviewing approximately 40 opportunities over nine months, ProVenEx is currently exploring investments in two early-stage biotechnology companies working on technologies in the contraceptive/anti-STD and vaccine areas. In both these areas, ProVenEx's primary interest lies in the potential of these technologies to 1) meet an unmet need for products that provide protection against HIV, other sexually-transmitted diseases, and other infectious diseases, and 2) result in products that would be made available to poor people in developing countries at an affordable price.

In addition, ProVenEx is in the early stages of exploring the feasibility of a public-private joint-venture with pharmaceutical, biotechnology and venture capital companies to develop and distribute new and existing drugs for infectious diseases in poor developing countries.

Lessons Learned

1. Few projects meet *both* philanthropic and investment criteria. It has been difficult to identify investment opportunities which can meet both the Foundation's philanthropic criteria and those of a venture capital investor. Most start-up or early-stage opportunities meet only one criterion, or neither.

2. Philanthropy and venture capital can create a viable partnership. Although it is too early to point to any outcomes, ProVenEx's early experience with Warburg Pincus and other private partners indicate that philanthropic and public sector interests can benefit from the discipline and focus of the venture capital model. On the other hand, philanthropic and public sector funding could lead to new and niche market opportunities for private sector partners, for example, the unmet need for anti-STD products among women could present a billion dollar global market for a product that is effective and easy to use. It is currently a market that is largely ignored by large pharmaceutical companies.

3. Non-monetary resources are equally important. For the viable investment opportunities, ProVenEx's potential ability to provide access to knowledgeable scientific experts, consultants, potential developing country partners, and potential co-investors will be as important as the funding that it will provide to the company.

4. Potential synergies with grant-giving activities. ProVenEx has been able to productively use the knowledge base and networks of researchers, scientists and experts that the Foundation has developed through its grants and partnerships with other foundations to identify promising new technological advances for potential investment. In addition, this knowledge base and networks will be valuable contributions to the portfolio companies' product development strategies.

5. Management. One of the common reasons why potentially promising technologies or ideas are nonetheless not considered to be viable investments is the absence of a management team or the difficulty of identifying a qualified management team to execute the business plan.

6. Flexibility. The ProVenEx strategy has had to be flexible and open to new investment structures, tools and partnerships in order to achieve its broad objective of accelerating new technologies and products for the benefit of the world's poor. In most cases, ProVenEx considers business plans submitted by newly established or expanding companies. However, in other cases, where gaps have been identified and where there are no existing entities, it is also exploring public-private partnerships to start up new entities.

Prepared by Jackie Khor, The Rockefeller Foundation

International Service for the Acquisition of Agri-Biotech Applications (ISAAA)

ISAAA's objective is the transfer and delivery of appropriate biotechnology products, particularly proprietary technology from the private sector in industrialized countries (the North) to developing countries (the South) by building partnerships between institutions in the South and the private sector in the North.

In the past, developing countries had access to non-proprietary technology from the public sector of the North. With the discovery and development of new biotechnology applications, this situation is changing. New technologies are increasingly proprietary, and are generally owned by corporations in the North.

ISAAA was created, in part, through the efforts of the Rockefeller Foundation. ISAAA is a non-profit organization financed by foundations, bilateral aid agencies, and corporations.

Strategy

ISAAA *facilitates* the development of partnerships for the safe and effective introduction of biotech applications that have already been tested in industrialized countries.
ISAAA functions through centers based at Cornell University in the US and the John Innes Centre in the UK, to monitor and evaluate the availability of biotechnology for transfer to the South.

It focuses on:

a) increasing the productivity of food crops, particularly commodities grown by resource-poor farmers, and contributing to sustainable agriculture and a safer environment through the development of alternatives to toxic pesticides;
b) tissue culture, diagnostics, and transgenic crops;
c) bio and food safety considerations and the responsible deployment of resistant genes; and
d) providing assistance in the complex area of intellectual property rights - a full time professional was appointed in late 1998 for this task.

Outcome

Over twelve ISAAA projects have been developed, brokered and implemented.
Monsanto donated coat protein genes to Mexico for the control of potato viruses (PVX/PVY). This project is funded by the Rockefeller Foundation and includes technology transfer and training of Mexican scientists. The first generation of transgenic potato developed by Mexican scientists has been field-tested in Mexico. Monsanto has agreed for Mexico to transfer the PVX/PVY technology to Kenya. More recently Monsanto has also agreed to ISAAA's request to provide Mexico with the gene that confers resistance to potato leaf virus (PLRV), the most important virus diseases of potatoes in Mexico ; the PLRV gene will be incorporated in potato varieties that are used by small resource poor farmers. An ex ante socio-economic study commissioned by ISAAA (ISAAA Brief No 7 1998) indicates that whereas the PVX/PVY/PLRV resistant potatoes can potentially cut production costs on large farms by 13 percent, the anticipated reduction costs in small farms is 32 percent ..

Other ISAAA projects that are being implemented or under negotiation include:

- Diagnostic for black rot crucifers, an important disease for cabbage in Asia (Washington State University and Asian Research and Development Center)
- Diagnostics for maize diseases in Brazil
  (Pioneer Hi-Bred Intl. and EMPRAPA)

- Tissue culture technology to increase productivity of bananas in Kenya (Public and Private Sector inputs of technology and know-how from organizations in South Africa
- Tissue culture/micropropagation technology to increase the productivity of the most important multiple purpose tree in Kenya (technology donated by Mondi Corporation of South Africa to Kenya and funded by the Gatsby Foundation , UK)
- Development of papaya that has delayed ripening genes that should result in significantly lower post harvest losses (Zeneca and the five ISAAA target countries in South East Asia viz Thailand, Indonesia Malaysia, Philippines and Vietnam)
- Development of papaya that is resistant to the most devastating disease of papaya in the developing world - papaya ring spot virus (technology donated by Monsanto to the five ISAAA target countries in South East Asia)
- Development of a transgenic sweet potato resistant to the most economically important virus disease in Kenya and in other countries of East Africa (Technology donated by Monsanto to Kenya)
- Development of several other projects in South East Asia featuring technology to increase productivity of orphan crops (projects under negotiation with several private sector companies including Novartis, AgrEvo and Dow AgroSciences)
- Insect resistant cotton
  (ISAAA facilitated discussions with Monsanto and institutions in Brazil, Argentina)
- Transfer of select marker genes in cassava
  (Sandoz/CIAT)

Other Programs
ISAAA offers forums for exchange of views between the public and private sectors through workshops on biosafety. It has undertaken research on intellectual property, biodiversity, and deployment and management of crops resistant to insects. Its fellowship programs have arranged for over twenty scientists to get hands-on training with private corporations.

Corporate Partners
AgrEvo (Germany), Asgrow (USA), Dow AgroScieneces (USA), Zeneca (UK), KWS (Germany), Monsanto (USA), Pioneer Hi-Bred International (USA), Novartis Seeds (Switzerland), and Schering (Germany) have committed or are in negotiation to donate technology and/or to provide training to scientists from developing countries under the aegis of ISAAA.

Lessons Learned
Different models of public-private partnerships can be negotiated:

a) The goodwill of private corporations can be tapped to secure access to proprietary technologies for use in resource-poor areas by means of donations to public sector institutions in the South.

b) Joint ventures between Northern and Southern institutions can be created when technologies are contributed by both partners (for instance, adapted germplasm from the South and a gene that confers added value from a Northern corporation with the understanding that developmental costs and return on investment will be shared).

Prepared by Sunil Chacko, Consultant, Rockefeller Foundation
Source: Agricultural Research and Development: The Need for Public-Private Sector Partnerships by Clive James. CGIAR. 1997.

Merck and Task Force for Child Survival and Development
Mectizan Donation Program (MDP) for Onchocerciasis Control

Onchocerciasis, also known as River Blindness, is the second largest infectious cause of blindness in the world (second to Trachoma). It is a chronic disease caused by the filarial worm Onchocerca volvulus. The disease is transmitted by the bite of infected female blackflies. Onchocerciasis is endemic in 35 countries, 28 of which are in Africa. 18 million people are infected with the disease. Almost 300,000 people are blind due to the disease and 6 million suffer from severe itching and dermatitis. Some 126 million people are at risk of the disease.

Researchers documented the devastating impact to local societies of blindness caused by onchocerciasis and how a single annual dose of Ivermectin (Mectizan) greatly reduces microfilarial loads. Although Ivermectin does not kill adult worms, the reduction in microfilariae density in the skin can interrupt transmission by black fly vectors, and hence is an effective control strategy.

Strategic Partnership
Merck and the Task Force on Child Survival and Development at the Carter Center
In 1987, Merck announced its intention to donate all the Ivermectin needed for onchocerciasis control. The drug was already a major success in the veterinary market, and Merck was doing exceptionally well in the late '80s. Merck partnered with the Task Force to create the Mectizan Donation Program (MDP). While international shipping costs are met by Merck, local distribution costs are the responsibility of local partners (NGOs, government, multilateral agencies).

The MDP distributes the Merck-donated Ivermectin to mass treatment programs in endemic countries. Governments or non-governmental organizations (NGOs) can apply to the MDP for Ivermectin. Once the application is processed, approval is sent to Merck's corporate contributions unit and then on to Merck's Export Department in France which ships the tablets to the recipient organizations.

The donation program involves several departments of Merck, the Task Force on Child Survival and recipient governments and NGOs:

a) *Mectizan Expert Committee*
The Committee, chaired by Dr. Bill Foege, is charged with facilitating the earliest and widest possible application of Mectizan in public health programs consistent with good medical practice in all areas where onchocerciasis is endemic. The Committee develops guidelines and standards for community treatment programs, and reviews new applications for tablets that must demonstrate i) endemicity in the proposed target population; ii) ability to bear the cost of distributing the drug; iii) endorsement by the country's Ministry of Health; iv) competent field program plans and capacity in patient registration, exclusion, dose determination, administration and post-treatment monitoring. The Committee also advises and assists applicants in the implementation of treatment

programs, and monitors progress. Monitoring is also to ensure that diversion of ivermectin to the veterinary black market in industrialized countries does not occur.

b) *The Mectizan Expert Committee Secretariat*
The Secretariat carries out the daily work of the Committee. The costs of both the Committee and its Secretariat are borne by Merck.

c) *Merck's Senior Director of Marketing Anti-Infectives*
Merck's Senior Director of Marketing Anti-Infectives is responsible for strategic planning, budgeting and implementation of MDP. He serves as the interface between Merck's senior management and the MDP. His budget covers the staff and administrative costs of the MDP.

d) *Merck's Corporate Contributions*
As of July 1998, more than 100 million Ivermectin treatments have been donated to treat an estimated 25 million people. Merck's budget for Corporate Contributions covers the actual donation, shipping costs and all of the administrative support costs.

e) *Merck's Export Department*
Merck's export department, based in Riom, France, ships the tablets to recipients, and works with governments to ensure that customs duties are not charged in endemic countries.

f) *Community Mass Treatment Programs*
A wide range of institutions and organizations are permitted to apply for free Ivermectin including Ministries of health, national, state or local governments, health care and public health organizations, hospitals or dispensaries that provide outreach, domestic or international NGOs, schools of medicine and related institutions, and industrial and employee health-care organizations. To date, 55% of the applications have been from NGOs, 35% from ministries of health, and 10% from the Onchocerciasis Control Program and academic institutions.

g) *Other important institutions* involved in onchocerciasis control have been the World Bank, responsible for fund-raising, the World Health Organization, the technical resource for program management, and the multi-donor supported Onchocerciasis Control Program (now called the African Program for Onchocerciasis Control, APOC)

Outcome
Ivermectin donation has been a resounding success with onchocerciasis well under control and removed as a public health threat from many areas. Merck has gained enormous goodwill through this donation program. The monitoring capacity that tracks movement of Ivermectin from Merck's facilities in France to the patient and the strict accounting for donated product prevents leakage. The program is an example of the power of coalitions reaching millions of people each month without a formal organizational structure. It is one of the most unique programs in global health today.

Lessons Learned

1) Leadership from Dr. Roy Vagelos, then Merck's Chairman, Dr. Bill Foege and former President Carter was critically important.
2) Philanthropic pursuits serve humanitarian, public relations and tax purposes. The marginal cost of producing additional quantities of Ivermectin for donation was within the boundaries of Merck's corporate contributions budget.
3) Careful monitoring can prevent leakage of donated products back to industrialized country black markets.

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Edna McConnell Clark Foundation and Pfizer, Inc.
International Trachoma Initiative (ITI)

Trachoma is the world's leading infectious cause of blindness. About 6 million people are blind because of the disease, and more than 150 million in the developing world need immediate treatment. Some 540 million people, about 10% of the world's population, are at risk of blindness or visual impairment through trachoma. The disease, caused by the bacteria Chlamydia trachomatis, usually begins early in childhood. Blindness occurs much later in life after repeated infections cause inversion of the eyelid and trauma to the cornea from contact with eye lashes.

Strategic Partnership
The International Trachoma Initiative (ITI)
The ITI is a $66 million program announced on November 10, 1998 by the Edna McConnell Clark Foundation and Pfizer, Inc. to eliminate blinding trachoma in five countries. Among the 46 countries where trachoma is endemic, the five likely to be included in this pilot program are: Morocco, Mali, Ghana, Tanzania, and Vietnam. The new initiative received widespread acclaim, including coverage in the New York Times, the Financial Times, and the Lancet.

The scientific basis for the new program is the joint work undertaken by the Clark Foundation and Pfizer, Inc., which determined that a single oral dose of Azithromycin (Zithromax) can treat trachoma. This is far superior to tetracycline, which has to be administered several times daily for 4-6 weeks as an irritating eye ointment. The International Trachoma Initiative is a 501 [c] 3 non-profit organization through which Pfizer's donation will be handled and which will build the partnerships in countries to deliver the product in conjunction with the *SAFE* strategy of community-based trachoma control. The *SAFE* strategy involves minor *S*urgery, *A*ntibiotics, *F*ace washing, and *E*nvironmental change.

What Each Partner Brings
The Edna McConnell Clark Foundation's Program for Tropical Diseases Research has over 20 years of experience working on infectious diseases in developing countries. The Foundation's sponsorship of the International Trachoma Initiative includes deploying its technical expertise, capacity for operational research, and the convening power to mobilize important groups for trachoma control. The Clark Foundation's Tropical Disease Program led by Dr. Joe Cook was instrumental in encouraging Pfizer to donate Zithromax.

Pfizer, Inc. will donate Zithromax (Azithromycin) for use in five developing countries. This expensive drug (costing approximately $30 per gram) is normally well beyond the budgetary reach of developing country trachoma control programs.

Governments will pay for local program costs, including health personnel salaries, vehicles/fuel, and social marketing efforts.

Multilateral agencies may provide loans to governments to enable them to meet local costs.

Many *non-governmental organizations (NGOs)*, such as Helen Keller International, will work with the Clark Foundation, Pfizer, Inc. and governments to deliver the drug to affected individuals.

Outcome
The ITI is a dynamic partnership that has brought benefits to people in many countries and hope for others. It has also served to inform stakeholders of Pfizer's and the Clark Foundation's commitment to eliminating blinding trachoma.

Lessons Learned
1) The trust between the Edna McConnell Clark Foundation and Pfizer was built over many years of successfully working together with NIAID on a trial in three countries and later in Morocco where Pfizer has been donating Zithromax.
2) Philanthropic pursuits serve humanitarian, public relations and tax purposes. The marginal cost of producing additional quantities of Azithromycin for donation was within the boundaries of Pfizer's corporate contributions budget.
2) Foundations can help to bridge scientific gaps by sponsoring niche studies that can reduce the burden of disease of low-income populations. These studies are unlikely to be a priority for major pharmaceutical companies preoccupied in R&D to produce billion-dollar drugs for application in paying populations as is required of them by their shareholders.

Additional Information on the core Partners:

The Edna McConnell Clark Foundation
The Foundation, with assets of over $560 million, ranks among the top 60 US foundations. In addition to trachoma, the Foundation works on child protection, student achievement, and on New York neighborhoods.

Pfizer
Pfizer profits were $2.6 billion on sales of $13.3 billion in 1998. Pfizer's research budget is $2 billion per year. Zithromax (Azithromycin), Pfizer's treatment for chlamydia and other bacterial infections has projected sales of $1.2 billion in 1999. Its patent as an antibiotic is valid until 2005. It is currently being tested to see if it can prevent heart attacks since a related chlamydia strain is found in the plaque that clogs arteries and causes heart attacks.
In the US, Pfizer, Inc. donates some drugs through "Sharing the Care," another public-private partnership working through 350 eligible community health centers.

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